Liver abscesses in adult patients with and without diabetes mellitus: an analysis of the clinical characteristics, features of the causative pathogens, outcomes and predictors of fatality: a report based on a large population, retrospective study in China

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Abstract

In China, there are four types of liver abscesses (LAs) that meet the clinical criteria. Pyogenic liver abscesses (PLAs) and amoebic liver abscesses (ALAs) are two of the most common types of abscesses, followed by fungal liver abscesses (FLAs) and hydatid secondary liver abscesses (HsLAs). Diabetes mellitus (DM) is associated with the development of PLAs. However, there is a lack of population-based studies that have evaluated the underlying relationship between LAs (mainly PLAs and FLAs) and DM. We conducted a retrospective study based on a large population to identify the potential differences and factors that affect the mortality of PLA patients in DM and non-DM groups. Our results revealed that the prevalence of DM is 44.3% (158/357) in PLA patients and 35.3% (18/51) in FLA patients. Compared with the non-DM patients, statistically significant differences were found in DM patients according to symptomatology, clinical manifestations, laboratory findings, microbiological characteristics, antimicrobial resistance, clinical treatments and outcomes in relation to mortality. In addition, the status of antibiotic resistance to *E. coli* and *K. pneumoniae*, which were isolated from the patient samples, is severe in the area in which the study was conducted. Regarding the treatment of PLAs, our study indicated that broad-spectrum antimicrobial therapy and drug combinations should be recommended and initiated before the pathogens are cultured and identified. In the clinic, therapies that combine percutaneous drainage with antibiotics and surgery with antibiotics are the two most useful strategies for treating an LA. These two combined treatments resulted in satisfactory cure rates. In the DM and non-DM groups, the cure rates for percutaneous drainage with antibiotics were 90.3% and 92.0%, respectively, and the cure rates for surgery with antibiotics were 93.9% and 95.2%, respectively.

Keywords: Amoebic liver abscess, antibiotic resistance, diabetes mellitus, *Escherichia coli*, fungal liver abscess, *Klebsiella pneumoniae*, liver abscess, outcomes, pyogenic liver abscess, treatments

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Introduction

A liver abscess (LA) is a common and potentially life-threatening disease in China and throughout the world, with an increasing incidence [1]. LAs often manifest as the result of an emerging infectious disease, which is typically associated with severe morbidity and mortality around the world. In China, the two most common types of LAs that have been observed in clinics are PLAs and ALAs. There is significant regional distribution of LAs all over the world; however, LAs are common throughout the world, with an incidence that varies from 0.006% to 2.2% of hospital admissions [2]. The incidence rate of hospitalization for an LA is different worldwide and increases annually. In Denmark and Canada, the incidence rate of PLAs was 1.1–2.3 cases per 100 000 individuals [3,4]. In the United States, the incidence rate

increased significantly from 2.7 to 4.1 cases per 100 000 individuals from 1994 to 2005 [1], and in Taiwan, the rate was 17.6 per 100 000 individuals [5]. The overall incidence of all of the types of LAs in the United States has been estimated to be 5–20 cases per 100 000 individuals. PLA cases represent approximately 80% of the LA cases in the United States and in Western countries; superinfection and ALA cases each represent 10% of the cases, and fungi and other organisms represent <10% of the cases [6]. Many studies have been conducted on LAs and their pathology, clinical treatments and outcomes [1–4,6]; however, there have been no correlative reports on the status of LAs in China, and the impact of this disease is unclear.

Patients with DM are at an increased risk of bacterial infection [7], which is a significant cause of clinical mortality among DM patients. DM, malignancy, renal disease and pneumonia are associated with a higher risk of LAs [5], and DM is a well-established risk factor for PLAs; however, little is known about the influence of DM on PLAs. Many studies have indicated that DM is a predisposing factor for PLAs, and patients with DM are more prone to developing PLAs than patients without DM [8–11]. Excluding PLAs, the prevalence and clinical features of other types of LAs (ALAs, FLAs and HsLAs) in DM and non-DM patients have not been described. A few studies have analyzed and compared the clinical characteristics and features of the causative pathogens of LAs in patients with DM and without DM [12]. Because there have been few clinical cases, most of the studies are case reports, and no studies have assessed bacterial culture and antimicrobial resistance in PLA patients with and without DM. In China, the annual incidence and clinical features of LAs need to be delineated.

More than 100 LA patients are admitted to our hospital (The First Affiliated Hospital of Harbin Medical University, FAH-HMU) annually. The FAH-HMU is an over 3000-bed teaching medical centre located in northeast China. We conducted a retrospective study on LA patients, including a comparison of the demographic characteristics, symptomatology, clinical manifestations, laboratory and imaging findings, microbiology of pathogenic bacteria, antimicrobial resistance testing, clinical outcomes and factors in relation to mortality between PLA patients who were assigned to DM and non-DM groups. In addition, we compared the treatments, clinical outcomes and mortality rates of FLA patients in the DM and non-DM groups. Parameters, such as the morbidity that is associated with all of the types of LAs, the characteristics of the pathogenic bacteria, liver function, clinical signs and symptoms, outcomes, such as the length of hospital stay, procedure-related complications and treatment failure or death were analysed.

Materials and Methods

Study design

A retrospective study based on a large population was conducted from February 2005 to August 2009.

Study patients and inclusion criteria

The medical ethics committee at FAH-HMU approved the protocol for the retrospective study, and all of the patients were informed of the retrospective review and signed informed consent forms before the clinical data were collected. All of the patients were over 16 years of age without gender or race restrictions. We retrospectively reviewed the medical and microbiological records of all of the patients who were hospitalized due to LAs and were treated at FAH-HMU from February 2005 to August 2009. Importantly, when the patients recovered, died or left the hospital, the discharged diagnoses were LAs, including PLAs, ALAs, FLAs and HsLAs, according to the medical records.

The patients who were included in our study met the following criteria: (i) a patient received complete and systematic treatment at FAH-HMU, and the medical files were complete; (ii) an LA was the primary cause of the hospitalization and treatment of a patient but not a complication; (iii) LAs that were primarily induced by a liver tumour or metastasis tumour were obviated; and (iv) no other extra-hepatic abdominal abscesses coexisted in the patient. After applying the inclusion and exclusion criteria to our study, a total of 596 patients were eligible for further analysis. A total of 16 LA patients were excluded from the study because their medical treatment data were missing. A total of 23 LA patients were obviated because they were transferred to different hospitals without receiving complete treatment at FAH-HMU. Most of the patients were from the Heilongjiang Province, Inner Mongolia and the Jilin Province.

A diagnosis of a PLA was defined as the following: (i) the presence of the typical clinical manifestations of infection, such as leukocytosis, fever, bacteraemia or sepsis and right upper abdominal pain; (ii) imaging evidence, including ultrasonography (US), computerized tomography (CT) or both US and CT and magnetic resonance imaging (MRI), and positive US-guided or CT-guided aspiration that was consistent with a PLA; (iii) laboratory findings, including white blood count, neutrophil granulocyte count, abnormal liver function and blood or pus culture; (iv) surgical findings; and (v) resolution of the lesion after experiential therapy with antibiotics if irrefutable evidence from the cultures or surgery was initially lacking.

A diagnosis of an ALA was defined as the following: (i) the presence of the typical clinical manifestations of amoebic

infection, such as leukocytosis, high fever, right upper abdominal pain and recent diarrhoea; (ii) imaging evidence, including US, CT or both, and positive US-guided or CT-guided aspiration that was consistent with an ALA; (iii) laboratory findings, including white blood count, neutrophil granulocyte count, abnormal liver function, increased erythrocyte sedimentation rate (ESR), amoeba trophozoites in stools or in aposematic material, positive findings on wet mount examinations or an entamoeba indirect haemagglutination test (E. IHA) antibody titre >1:75; (iv) surgical findings; and (v) resolution of the lesion after experiential therapy with antiamoebic drugs if irrefutable evidence was lacking in the results.

A diagnosis of an FLA was defined as the following: (i) the presence of the clinical manifestations of fungal infection, such as leukocytosis, fever and right upper abdominal pain, which are insensitive to antibiotic treatment; (ii) imaging evidence, such as abnormal CT, US or MRI; (iii) positive fungal growth from the abscess or blood cultures; (iv) evidence of fungal hepatic infection found during the autopsy.

A diagnosis of an HsLA was defined as the following: (i) the presence of the clinical manifestations of an HsLA, such as hepatomegaly and right upper abdominal pain, contact with livestock or house pets, such as a dog, particularly a shepherd dog, sheep, horse or pig; (ii) imaging evidence, such as abnormal CT, US or MRI; (iii) increased eosinophil granulocyte count, indirect haemagglutination test that is positive for IgM, positive Weinberg complement fixation test and positive Casoni test; and (iv) evidence of an HsLA found during surgery.

The patients who were included in the study were divided into two groups (a DM group and a non-DM group) according to whether they had contracted DM. The definition of DM was established according to the following criteria from 1997: a history of DM or the typical symptoms of DM, casual blood glucose concentrations ≥200 mg/dL, fasting plasma glucose ≥126 mg/dL, or 2-h plasma glucose ≥200 mg/dL during an oral glucose tolerance test [13].

Data source

All of the parameters that were included in the investigation were collected seriatim by reviewing the patient medical records that were preserved in the medical record library and the medical computerized database at FAH-HMU. The patient records were retrospectively examined for the primary set of data, which included demographic characteristics (age and sex), clinical parameters (signs and symptoms), laboratory values (haematologic, biochemical and microbiological findings), radiological findings (solitary or multiple abscesses and lobar distribution), concomitant diseases, diagnoses, treatment procedures, medications, catheter drainage, outcomes at discharge (recovered or died), admission and discharge dates, length of hospital stay and hospital mortality. All of the diagnoses, concomitant diseases and treatment procedures in the medical records were coded by the International Classification of Diseases, 9th Version, Clinical Modification (ICD-9-CM). According to the ICD-9-CM diagnosis codes, we identified 357 patients who were discharged with a diagnosis of a PLA (572.0) during the study period.

When the temperature of a patient was over 38.0°C, blood samples were taken for aerobic and anaerobic cultures. All the drained pus samples were taken for culture regardless of the patients' temperatures during their hospital stays. Upon admission to the hospital, patients were promptly treated with empirical, broad-spectrum antibiotics before the initial drainage procedure, depending on the clinical presentation; however, once the results of the culture and susceptibility tests were obtained, the antibiotic treatment was modified according to them. Most of the patients underwent catheter drainage unless the LAs were too small to require drainage (<3 cm) or there were technical difficulties; however, empirical antibiotics were prescribed to patients upon admission to the hospital regardless of whether catheter drains were employed. The drains remained in place until the convalescent stage. Surgery was the last treatment option and was performed in several emergency cases, such as an abscess rupture.

During hospitalization, patient complications, such as a cardiovascular system occurrence (CVSO), for example acute coronary artery syndrome, myocardial infarction, hypertension, lacunar cerebral infarction and haemorrhagic stroke were analysed. The follow-up of all of the recovered patients was conducted at outpatient clinics or by telephone or e-mail. Recurrence was concluded when a patient returned to the hospital because of an LA within 1 year of discharge.

The microbiological parameters that were included in our study consisted of polymicrobial infection, monomicrobial infection (*K. pneumoniae* or *E. coli*), anaerobic infection, bacteraemia and multidrug-resistant (MDR) isolates. Polymicrobial infection was defined as the presence of two or more pathogens that were cultured from blood or pus specimens. Anaerobic infection was concluded when anaerobic isolates were cultured from blood or pus. MDR was defined as resistance to three or more of the antimicrobial classes. An abscess specimen was obtained using the following invasive procedures: image-guided (US or CT) percutaneous needle aspiration (PNA), image-guided percutaneous catheter drainage (PCD) or a surgical approach. All of the pus and blood specimens were processed for bacterial culture and Gram stain. The isolated pathogens were tested for antimicrobial susceptibility.

Because PLAs account for a large proportion of LAs and *K. pneumoniae* and *E. coli* were the two most common pathogenic bacteria at the clinic, we focused on understanding PLAs and the microbiological characteristics of these two cultured bacteria. To provide guidance to clinicians on utilizing antibiotics for the treatment of PLAs, we detected extended-spectrum β-lactamase (ESBL) in the isolated strains of *E. coli* and *K. pneumoniae* using an ATB microbiological system. We selected the Kirby-Bauer (K-B) method for the antimicrobial susceptibility testing. The results were evaluated according to the National Committee for Clinical Laboratory Standards (NCCLS, USA, 2005), and WHONET 5 was employed to analyse the drug sensitivities to the *E. coli* and *K. pneumoniae* strains that were isolated from the pus and blood cultures.

Regarding mortality, a logistic regression model was developed to analyse the relationship between the significant variables (such as diabetes mellitus, Gas-forming, polymicrobial infection, multidrug resistance, and so on) and mortality. The symptoms and signs were excluded from the analysis because the characteristics of these data were subjective.

Statistical analysis

The statistical analysis was performed using the SAS statistical software package (SAS, version 9.1; SAS Institute Inc., Cary, NC, USA). The descriptive data were presented as the means with standard deviations (SDs) for the continuous data and as percentages for the categorical data. The chi-squared test or Fisher's exact test were used to evaluate the differences in the categorical variables; Student's *t*-test was used to evaluate the differences in the continuous variables. A logistic regression model was developed to identify the independent prognostic factors that were associated with mortality. The odds ratios (ORs) and 95% confidence intervals (95% CIs) were estimated in the logistic regression model. $p < 0.05$ was considered statistically significant in all of the analyses. All of the p values were two tailed.

Results

Characteristics of the patients and descriptive tables and data

Overall, a total of 596 medical records of patients who were discharged with a diagnosis of an LA or a diagnosis that was related to an LA were retrieved. After excluding 39 patients whose medical data were incomplete, a total of 557 patients who met the selection criteria were included in the final analysis. None of the patients was seropositive for HIV. Of the 557 patients who were included in the analysis, 238 (42.7%) patients had DM. The cohort was mainly composed of four types of LAs, including PLAs, ALAs, FLAs and HsLAs. The demography of the LA cases and the numbers of our study subjects are listed in Table 1. The results of the study are expounded in sequence.

TABLE 1. Demographic characteristics of the liver abscesses in patients with diabetes mellitus (DM) and without diabetes mellitus (non-DM)

Liver abscess type	DM cases (%)	Non-DM cases	p value (χ^2-test)
PLA	158	199	
Male	93 (58.9)	108 (54.3)	0.385
ALA	11	95	
Male	7 (63.6)	69 (72.6)	0.502
FLA	18	33	
Male	8 (44.4)	17 (51.5)	0.629
HsLA	15	28	
Male	6 (40.0)	10 (35.7)	0.782
Total	202 (36.3)	355 (63.7)	–

Pyogenic liver abscess

Patient demographic data, recent medical history, pathogenesis, complications, lesion size and location.

Excluding the patients who did not meet the inclusion criteria, a total of 357 patients who were ≥16 years of age received complete treatment for a PLA during the study period. Of the included PLA patients, 158 (44.3%) patients had DM, and 201 patients were male (male-to-female ratio, 1.29:1.0). Among the diabetic PLA patients, 28 (17.7%) patients were diagnosed with DM during their hospitalization for a PLA. None of the patients had developed ketoacidosis after admission according to the medical records. The 357 patients with a PLA represented approximately 0.16% of the patients who were admitted to the hospital (160 cases per 100 000 admissions) during the period. We found that more co-morbidities were present in diabetic patients than in non-diabetic patients, such as a higher prevalence rate of the common cold within 2 weeks before admission according to the personal histories. Compared with the DM group, PLA patients without DM were more prone to coexisting malignancy, and these patients had lower prevalence rates of coexisting cardiovascular system diseases. The most frequent aetiopathogenesis of a PLA in both groups was a cryptogenic origin; however, this origin was more common in the DM group. A biliary origin (biliary calculi and/or cholecystolithiasis) was the second most common aetiology; however, the frequency of this origin was less in the DM group than in the non-DM group. The differences in the sizes and locations of the LA lesions between the two groups were statistically significant. Moreover, the DM group had a higher prevalence of a gas-forming PLA (p 0.026), and the patients with DM had a greater tendency to have multiple abscesses (p 0.023). The

rates of MODS and abscess recurrence were higher in the DM group than in the non-DM group. Statistically significant differences were found between the DM and non-DM groups according to the duration of stay in the intensive care unit (ICU-T) and the total average febrifacient time (t-AFT). In addition, patients who developed a PLA after blunt abdominal traumas, such as vehicle collisions, that caused liver lacerations were classified as 'liver traumas'. Two patients developed a PLA after percutaneous transhepatic cholangiography and drainage, and these patients were classified as 'other'. (Table 2).

Patient clinical symptoms and signs.

The most common symptoms of a PLA were fever and chills in both groups, followed by right upper quadrant (RUQ) pain, nausea and vomiting and general weakness. The prevalence rates of the other symptoms and signs listed in Table 2 were under 20%. More PLA patients with DM had temperatures >38.5°C than patients without DM (p 0.035). Nausea and vomiting were more common in the DM group than in the non-DM group (p 0.005). In addition, the DM patients had higher prevalence rates of systemic inflammatory response syndrome (SIRS, p 0.044) and shock (p 0.026) during hospitalization. (Table 3).

Patient laboratory and imaging findings.

The following blood test findings were similar for most of the patients in both groups: leukocytosis (always with a left shift), changes in haemogram, abnormal liver function and anaemia. We detected five biochemical indicators, such as leukocytosis, blood urea nitrogen (BUN), creatinine (Cr), hypoproteinaemia and temporarily increased ESR, which demonstrated statistically significant differences between the two groups. A higher incidence of anaemia, neutrophilic pleocytosis, prolonged prothrombin time (PT) and elevated AST and/or ALT levels was detected in both groups; however, there were no statistical differences. Additionally, increased serum levels of alkaline phosphatase (ALP) and gamma-glutamyltransferase (GGT) were observed in more than 50% of the patients in both groups; however, the difference was not statistically significant. Remarkably, the sensitivity of the cross-reacting protein (CRP) was approximately 100% in all of the PLA patients. All of the diagnostic modalities (US, CT or MRI) that were employed for a PLA had a sensitivity of over 95% in both groups of patients. (Table 4).

Patient microbiological findings and the status of antibiotic resistance in the cultured bacteria.

Microbiological findings: Pus cultures were collected in 86.3% ((140 + 168)/357) of the patients, and the overall positive growth rate was 91.2% ((131 + 150)/(140 + 168)). The positive growth rates in the DM and non-DM groups were 93.6% and 89.3%, respectively. The overall rate of polymicrobial growth in the pus cultures was 9.7% ((16 + 14)/(140 + 168)), and the rates in the DM and non-DM groups were 12.2% and 9.3%, respectively; however, the difference was not statistically significant. During hospitalization, when the temperature of a patient was over 38.0°C, blood

TABLE 2. Characteristics of the recent patient histories before admission, pathogenesis and complications during hospitalization of PLA patients with diabetes mellitus and without diabetes mellitus (non-DM)

Characteristics/ Demographics	DM cases 158 (%)	Non-DM cases 199 (%)	p value (χ^2-test)
Age (year, mean ± SD)	63.8 ± 15.7	57.2 ± 16.3	0.024[a]
PMH (within 2 weeks)			
Common cold	16 (10.1)	9 (4.5)	0.039
URTI	5 (3.2)	7 (3.5)	0.854
Community-acquired pneumonia	4 (2.5)	6 (3.0)	1.0[b]
Steroid use	5 (3.2)	4 (2.0)	0.517[b]
ISA use	2 (1.3)	3 (1.5)	1.0[b]
Malignancy	6 (3.8)	18 (9.0)	0.049
Radiotherapy	1 (0.6)	4 (2.0)	0.388[b]
Chemotherapeutics	7 (4.4)	11 (5.5)	0.638
Uraemia	5 (3.2)	7 (3.5)	0.854
Hepatitis (HB or HC)	11 (7.0)	15 (7.5)	0.835
Liver cirrhosis	9 (5.7)	13 (6.5)	0.744
Hepatic cyst	6 (3.8)	1 (0.5)	0.047[b]
Biliary tract disease	27 (17.1)	23 (11.6)	0.135
Appendicitis	2 (1.3)	2 (1.0)	1.0[b]
Other	–	–	NS
Pathogenesis			
Cryptogenic	124 (78.5)	120 (61.3)	<0.001
BC or CC	10 (6.3)	46 (23.1)	<0.001
SSTIs	9 (5.7)	7 (3.5)	0.323
Furuncle or carbuncle	5 (3.2)	4 (2.0)	0.517[b]
Direct invasion	2 (1.3)	3 (1.5)	1.0[b]
Liver trauma	4 (2.5)	3 (1.5)	0.70[b]
Other	4 (2.5)	16 (8.0)	NS
Abscess location			
Right lobe	80 (50.6)	117 (58.8)	0.018
Left lobe	40 (25.3)	57 (28.6)	
Bilobar involvement	38 (24.1)	25 (12.6)	0.005
Abscess size			
Single abscess			
<5	61 (38.6)	104 (52.3)	0.029
5–10	50 (31.6)	58 (29.1)	
>10	20 (12.7)	19 (9.5)	
Multiple abscesses	27 (17.1)	18 (9.1)	0.023
Gas-forming	18 (11.4)	10 (5.0)	0.026
COMP during DHS			
CVS occurrence	28 (17.7)	19 (9.5)	0.023
Reactive pleural fluid	11 (7.0)	15 (7.5)	0.835
Bacteraemia	77 (48.7)	89 (44.7)	0.450
Septic shock	9 (5.6)	13 (6.5)	0.744
Ascites	4 (2.5)	7 (3.5)	0.761[b]
ARF	3 (1.9)	4 (2.0)	1.0[b]
MODS	12 (7.6)	6 (3.0)	0.049
RC-A	20 (12.7)	13 (6.5)	0.047
t-AFT	15.4 ± 5.7	12.8 ± 9.6	0.012[a]
ICU-T	6.2 ± 3.9	4.3 ± 1.5	0.021[a]

SSTIs, skin and soft tissue infections; URTI, upper respiratory tract infection; CAP, community-acquired pneumonia; BC or CC, biliary calculi or cholecystolithiasis; ISA, immunosuppressive agent; COMP, complication; DHS, duration of hospital stay; CVS, cardiovascular system; ARF, acute renal failure; MODS, multi-organ dysfunction syndrome; RC-A, recurrence of the abscess; t-AFT, total average fever time; ICU-T, stay in intensive care unit (days); NS, not significant.
[a]Student's *t*-test.
[b]Fisher's exact test.

TABLE 3. Symptomatology of PLA patients with diabetes mellitus and without diabetes mellitus (non-DM)

Symptoms and signs	DM cases 158 (%)	Non-DM cases 199 (%)	p value (χ^2-test)
Symptoms			
Fever/chills	136 (86.1)	180 (90.5)	0.198
Cough/dyspnoea	13 (8.2)	16 (8.0)	0.949
General weakness	18 (11.4)	25 (12.6)	0.736
Hiccups	4 (2.5)	4 (2.0)	0.736[a]
Nausea/vomiting	36 (22.8)	23 (11.6)	0.005
Pleuritic/chest pain	9 (5.7)	12 (6.0)	0.894
RUQ pain	75 (47.5)	104 (52.3)	0.368
Abdominal pain	15 (9.5)	20 (10.0)	0.861
Diarrhoea	5 (3.2)	4 (2.0)	0.517[a]
Weight loss (≥2.5 kg)	11 (7.0)	10 (5.0)	0.440
Signs			
Fever (T ≥ 38.5°C)	27 (17.1)	19 (9.5)	0.035
Jaundice	6 (3.8)	10 (5.0)	0.578
Rales/rhonchi	11 (7.0)	13 (6.5)	0.872
Hepatomegaly	10 (6.3)	12 (6.0)	0.907
Murphy signs	5 (3.2)	11 (5.5)	0.284
Ascites	15 (8.0)	10 (5.0)	0.100
SIRS	11 (7.0)	5 (2.5)	0.044
Shock	8 (3.8)	2 (2.0)	0.026[a]

RUQ, right upper quadrant of abdomen; SIRS, systemic inflammatory response syndrome.
[a]Fisher's exact test.

TABLE 4. Laboratory and imaging findings of PLA patients with diabetes mellitus (DM) and without diabetes mellitus (non-DM)

Characteristics	DM cases 158 (%)	Non-DM cases 199 (%)	p value (χ^2-test)
Laboratory feature			
WBCc >10 000/dL	125 (79.1)	138 (69.3)	0.037
WBCc <4000/μL	5 (3.2)	7 (3.5)	0.854
Neutrophil count (>75%)	140 (88.6)	180 (90.1)	0.570
Platelet count (<140 000/dL)	10 (6.3)	19 (9.5)	0.269
Haemoglobin (<12 g/dL)	104 (65.8)	135 (67.8)	0.687
AST >50 IU/L	80 (50.6)	105 (52.7)	0.689
ALT >50 IU/L	89 (56.3)	122 (61.3)	0.342
PT >13.0 s	110 (69.6)	128 (64.3)	0.291
T. Bil >5 mg/dL	75 (47.5)	98 (48.7)	0.738
BUN >22 mg/dL	72 (45.6)	54 (27.1)	0.001
Cr >140 μM	58 (36.7)	52 (26.1)	0.032
CRP >6 mg/L	158 (100)	197 (99.0)	0.505[a]
Glucose > 120 mg/dL	146 (92.4)	57 (28.6)	<0.001
ESR >30 mm/h	64 (40.5)	58 (29.1)	0.025
ALP ≥3-fold	103 (65.2)	121 (60.8)	0.395
GGT ≥3-fold	87 (55.1)	116 (58.3)	0.541
Albumin <35 g/dL	37 (23.4)	27 (13.6)	0.016
Chest X-ray			
Pneumonia	12 (7.6)	14 (7.0)	0.840
Right pleural effusion	11 (7.0)	15 (7.5)	0.853
e-RHD	4 (2.5)	5 (2.5)	1.0[a]
Abnormal image (liver)			
Sonography	133/138 (96.4)	173/182 (95.1)	0.567
CT	118/120 (98.3)	140/143 (97.9)	1.0[a]
MRI	68/70 (97.1)	83/85 (97.6)	1.0[a]

WBCc, white blood cell count; AST, aspartate aminotransferase; ALT, alanine aminotransferase; PT, prothrombin time; T. Bil, total bilirubin; BUN, blood urea nitrogen; Cr, creatinine; CRP, cross-reacting protein; ESR, erythrocyte sedimentation rate; ALP, alkaline phosphatase; GGT, gamma glutamyl transpeptidase; e-RHD, elevated right hemidiaphragm; CT, computed tomography; MRI, magnetic resonance imaging.
[a]Fisher's exact test.

specimens were collected for anaerobic and/or aerobic cultures. The overall positive growth rate was 63.5% ((68 + 52)/(92 + 97)) in the blood cultures, and the positive

TABLE 5. Microbiological characteristics of PLA patients with diabetes mellitus (DM) and without diabetes mellitus (non-DM) during hospitalization: pus cultures

Characteristics	DM cases 140 (%)	Non-DM cases 168 (%)	p value (χ^2-test)
Positive growth	131 (93.6)	150 (89.3)	0.185
Polymicrobial growth	16 (12.2)	14 (9.3)	0.362
Klebsiella pneumonia	115 (87.8)	109 (72.7)	0.001
Klebsiella oxytoca	5 (3.8)	7 (4.7)	0.788
Anaerobe	9 (6.9)	2 (1.3)	0.014[a]
Bacteroides fragilis	1 (0.8)	1 (0.7)	1.0[a]
Escherichia coli	16 (12.2)	22 (14.7)	0.658
Staphylococcus aureus	4 (3.1)	4 (2.7)	1.0[a]
Viridians streptococcus	3 (2.3)	13 (8.7)	0.028
Pseudomonas aeruginosa	3 (2.3)	4 (2.7)	1.0[a]
Enterobacter faecalis	2 (1.5)	6 (4.0)	0.299[a]
Proteus mirabilis	2 (1.5)	3 (2.0)	1.0[a]
Enterococcus species	1 (0.8)	0 (0)	0.455[a]
Actinomycetes	0 (0)	2 (1.3)	0.503[a]
Others	–	–	NS

NS, not significant.
[a]Fisher's exact test.

growth rates in the DM and non-DM groups were 73.9% and 53.6%, respectively. The differences were statistically significant (p 0.004). A small proportion (5.3%, (6 + 4)/(92 + 97)) of the culture-positive patients had polymicrobial growths, and the number of bacteria that were isolated from the blood cultures was less than that from the pus cultures. Of the pathogens that were identified in the blood cultures of both groups, *K. pneumoniae* was the most commonly isolated pathogen, followed by *E. coli*. In the pus cultures of the DM group, *K. pneumoniae* was predominant, followed by *E. coli* and anaerobes, whereas *E. coli* and *Viridans streptococci* were the second and third most commonly isolated pathogens in the non-DM group. Anaerobes were only cultured and isolated from the pus specimens, and the growth rate of the anaerobes in the DM group was greater than that in the non-DM group. Conversely, the growth rate of *Viridians streptococci* in the pus and blood cultures in the non-DM group was greater than that in the DM group. The prevalence of other cultured bacteria was <5%, and we did not perform any further analysis (Tables 5 and 6).

Antibiotic resistance: In total, 338 bacterial pathogens (53 *E. coli* and 285 *K. pneumoniae*), which were cultured and isolated from PLA specimens, were analysed. We reviewed the patient medical records to obtain the results of the antimicrobial resistance testing. The state of antimicrobial resistance of cultured and isolated pathogens is very serious. The results of the susceptibility and resistance testing for the bacteria that were isolated from the specimens of both groups were examined.

The isolated *E. coli* strains were resistant to most of the common antibiotics that were used at the clinic and the rate of

TABLE 6. Microbiological characteristics of PLA patients with diabetes mellitus (DM) and without diabetes mellitus (non-DM) during hospitalization: blood cultures

Characteristics	DM cases 68 (%)	Non-DM cases 52 (%)	p value (χ^2-test)
Positive growth	68 (68/92,73.9)	52 (52/97,53.6)	0.004
Polymicrobial growth	6 (8.8)	7 (13.5)	0.418
Klebsiella pneumonia	59 (86.8)	39 (75.0)	0.099
Escherichia coli	2 (2.9)	13 (25.0)	<0.001[a]
Proteus mirabilis	1 (1.5)	0 (0)	1.00[a]
Pseudomonas aeruginosa	0 (0)	2 (3.8)	0.186[a]
Staphylococcus aureus	2 (2.9)	1 (1.9)	1.0[a]
Viridians streptococcus	1 (1.5)	4 (7.7)	0.165[a]
Enterobacter faecalis	1 (1.5)	3 (5.8)	0.315[a]

[a]Fisher's exact test.

resistance was remarkably high. The incidence of MDR bacteria in diabetic patients was higher than that in patients without DM. According to the ESBL test, 62.5% of the isolates were positive in the DM group, and 24.1% of the isolates were positive (p 0.005) in the non-DM group. The rate of resistance to gentamicin was significantly different between the DM and non-DM groups (p 0.011). In addition, differences in the rates of resistance were found for cefazolin (p 0.004), ciprofloxacin (p 0.014) and trimethoprim/sulfa (p 0.013).

The isolated *K. pneumoniae* strains were resistant to most of the common antibiotics that were used at the clinic, with high rates of resistance. According to the ESBL test, the rates of positive isolates in the DM and non-DM groups were 52.0% and 27.2%, respectively. The difference was statistically significant (p <0.001). The incidence of drug-resistant bacteria in the DM group was higher than that in the non-DM group, and the rate of resistance to antibiotics of the isolated *K. pneumoniae* strains was significantly different between the DM and non-DM groups. These differences were presented as amikacin (p 0.005), cefoperazone/sulbactam (p 0.001), cefazolin (p <0.001), levofloxacin (p < 0.001) and piperacillin/tazobactam (p 0.006). In addition, the majority of the *K. pneumoniae* strains that were isolated from the DM group were found to be resistant to gentamicin (55.1%), cefuroxime (52.8%), ciprofloxacin (63.8%) and piperacillin (76.4%). Accordingly, the rates of resistance to the four antibiotics in the non-DM group were lower: gentamicin (51.3%), cefuroxime (46.2%), ciprofloxacin (55.1%) and piperacillin (67.7%). The data regarding the antimicrobial resistance of the two isolated bacteria are listed in Tables 7 and 8.

TABLE 7. Microbiological characteristics of PLA patients with diabetes mellitus (DM) and without diabetes mellitus (non-DM) during hospitalization: antibiotic susceptibility and resistance testing of *Escherichia coli*

Antibiotic species	DM cases 24 (%)	Non-DM cases 29 (%)	p value (χ^2-test)
ESBL test	15 (62.5)	7 (24.1)	0.005
Plasmid-AmpC-β-lactamases	3 (12.5)	2 (6.9)	0.649[a]
Metallo-β-lactamases	0 (0)	0 (0)	NS
Amikacin	3 (12.5)	3 (10.3)	1.0[a]
Gentamicin	21 (87.5)	16 (55.2)	0.011
Cefazolin	12 (50.0)	4 (13.8)	0.004
Cefoxitin	18 (75.0)	26 (89.7)	0.271
Cefuroxime	23 (95.8)	27 (93.1)	1.0[a]
Ceftriaxone	7 (29.2)	5 (17.2)	0.302
Ceftazidime	9 (37.5)	7 (24.1)	0.292
Cefoperazone/sulbactam	4 (16.7)	5 (17.2)	1.0[a]
Cefepime	9 (37.5)	8 (27.6)	0.441
Ciprofloxacin	18 (75.5)	12 (41.4)	0.014
Levofloxacin	20 (83.3)	27 (93.1)	0.392
Imipenem	0 (0)	0 (0)	NS
Meropenem	0 (0)	0 (0)	NS
Aztreonam	8 (33.3)	7 (24.1)	0.459
Piperacillin	21 (87.5)	22 (75.9)	0.318
Piperacillin/tazobactam	2 (8.3)	2 (6.7)	1.0[a]
Trimethoprim/sulfa	22 (91.7)	18 (72.4)	0.013
Nitrofurantoin	5 (20.8)	4 (13.8)	0.715[a]

ESBL test, extended-spectrum β-lactamases test; NS, not significant.
[a]Fisher's exact test.

TABLE 8. Microbiological characteristics of PLA patients with diabetes mellitus (DM) and without diabetes mellitus (non-DM) during hospitalization: antibiotic susceptibility and resistance testing of *Klebsiella pneumoniae*

Antibiotic species	DM cases 127 (%)	Non-DM cases 158 (%)	p value (χ^2-test)
ESBL test	66 (52.0)	43 (27.2)	<0.001
Plasmid-AmpC-β-lactamases	16 (12.6)	12 (7.6)	0.158
Metallo-β-lactamases	0 (0)	0 (0)	NS
Amikacin	26 (20.5)	14 (8.9)	0.005
Gentamicin	70 (55.1)	81 (51.3)	0.517
Cefazolin	96 (75.6)	68 (43.0)	<0.001
Cefoxitin	38 (29.9)	43 (27.2)	0.615
Cefuroxime	67 (52.8)	73 (46.2)	0.271
Ceftriaxone	33 (26.0)	28 (17.7)	0.091
Ceftazidime	31 (24.4)	27 (17.1)	0.127
Cefoperazone/sulbactam	28 (22.0)	13 (8.2)	0.001
Cefepime	14 (11.0)	12 (7.6)	0.318
Ciprofloxacin	81 (63.8)	87 (55.1)	0.137
Levofloxacin	73 (57.5)	41 (25.9)	<0.001
Imipenem	8 (6.3)	5 (3.2)	0.207
Meropenem	5 (3.9)	3 (1.9)	0.473[a]
Aztreonam	9 (7.1)	8 (5.1)	0.473
Piperacillin	97 (76.4)	107 (67.7)	0.107
Piperacillin/tazobactam	21 (16.5)	10 (7.0)	0.006
Trimethoprim/sulfa	91 (71.7)	101 (63.9)	0.167
Nitrofurantoin	67 (52.8)	81 (51.3)	0.802

ESBL test, extended-spectrum β-lactamases test; NS, not significant.
[a]Fisher's exact test.

Amoebic liver abscess

During the study period, there were 106 patients over 16 years of age who had received complete treatment for an ALA at our hospital. Of the ALA patients, 11 (10.4%) patients had DM, 76 patients were male (male-to-female ratio, 2.5:1), and the mean age was 43.2 ± 3.2 years. The mean age of the patients without DM was 40.6 ± 4.1 years. In the histories of both groups of patients, diarrhoea was present in 36.4% (4/11) of the DM patients but 15.8% (15/95) of the non-DM patients; however, the difference was not

statistically significant. A difference (18.2% (2/11) vs. 36.8% (35/95)) in the prevalence of alcohol use was found between the two groups; however, the difference was not statistically significant. Remarkably, we found that ALAs in diabetic patients often developed into mixed infections ([45.5% (5/11) vs. 9.5% (9/95), p 0.006)). The majority of the abscesses in patients were detected in the right lobe. A single abscess with a diameter ≤5 cm was found in more than one-third of the patients in both groups whereas the prevalence of large abscesses (a diameter ≥10 cm) in the DM group was higher than that in the non-DM group (27.3% (3/11) vs. 15.8% (15/95)). During hospitalization, the prevalence of CVSO in the DM group was found to be higher than that in the non-DM group (18.2% (2/11) vs. 5.3% (5/95)), and the difference was not statistically significant. In this report, we only discussed the demographic characteristics of the patients with an ALA in both groups. The data regarding the symptomatology and the laboratory and imaging findings in both groups would need to be included in a separate article.

Fungal liver abscess

After a review of the medical records, a total of 51 FLA patients (male-to-female ratio, approximately 1:1) were included in this study. The mean ages of the FLA patients in the DM and non-DM groups were 66.7 ± 10.5 and 65.6 ± 12.9 years, respectively. In both groups, the majority of the abscesses were located in the right lobe. The diameters of most of the abscesses were <5 cm in both groups. Approximately one-third (30.3%) of the patients in the non-DM group had multiple abscesses whereas more than one-third (38.9%) of the patients in the DM group had multiple abscesses. In addition, the prevalence of CVSO in the DM group was higher than that in the non-DM group (27.8% vs. 12.1%). The incidence rates of MODS in the DM and non-DM groups were high (44.4% vs. 36.4%). The most common pathogen that was isolated from FLA patients was *Candida albicans*, followed by *Candida glabrata* in the DM group and *Candida mycoderma* in the non-DM group. Patients with DM were more prone to infection with *Candida glabrata* (38.9% (7/18) vs. 9.1% (3/33), p 0.023). The data regarding the characteristics of the patients with FLA would need to be included in a separate article.

In this study, the mortality rate (MR) of the PLA patients with DM was 7.6%, and the rate was 6.5% in the patients without DM; however, this difference was not statistically significant. For the PLA patients, there was no statistically significant difference in the achievement ratio of treatment between the DM and non-DM groups. For the FLA patients, the mortality rate was 38.9% and 24.2% for the DM group and non-DM group, respectively; however, this difference was not statistically significant. Similar results were obtained for the ALA patients, and no statistical differences were found in the outcomes of the two groups of patients (data not presented). In the FLA patients, the achievement ratio of treatment between the two groups was similar, excluding those patients who had accepted therapeutic alliance (SG + Ab). The different clinical outcomes in the DM and non-DM groups corresponded to the different LA types, and the variations among these types generally influence the clinical outcome of a patient. We found that DM demonstrated a negative impact on the clinical outcomes of the PLA and FLA patients, such as mean draining time (MDT), length of stay at the hospital and the duration of symptoms. The data on the MRs, achievement ratios of treatment and the clinical outcomes of the two groups of patients with PLA and FLA are shown in Tables 9 and 10.

TABLE 9. Comparison of the treatments, clinical outcomes and mortality rates (MRs) of PLAs between patients with diabetes mellitus (DM) and without diabetes mellitus (non-DM)

MR/Treatments / Clinical outcomes	DM cases 158 (%)	Non-DM cases 199 (%)	p value
MR	12 (7.6)	13 (6.5)	0.696
Treatments			
Ab	21 (13.3)	33 (16.6)	0.389
PD + Ab	113 (71.5)	147 (73.9)	0.620
SG + Ab	24 (15.2)	19 (9.5)	0.104
Outcomes			
m-TT	14.5 ± 8.8	10.2 ± 16.7	0.046[a]
LOS (day)	30.6 ± 17.3	23.2 ± 11.5	0.037[a]
PS	25.3 ± 13.6	17.1 ± 10.3	0.032[a]
AAT	22.3 ± 14.3	19.3 ± 11.2	0.622[a]

MR, mortality rate; Ab, antibiotic; PD, percutaneous tube drainage; SG, surgery; LOS, length of stay at hospital; PD + Ab, percutaneous tube drainage + antibiotic; SG + Ab, surgery + antibiotic; m-TT, mean tubing time; PS, persistence of symptoms (since patients accepted clinical treatments); AAT, antibiotic administration time.
[a]Student's *t*-test.

Discussion

To our knowledge, this is the first large population-based retrospective study to investigate the incidence, clinical characteristics, microbiological features and outcomes of PLA hospitalization for patients with and without DM. This investigation has provided a comprehensive perspective of the morbidity, mortality and clinical and epidemiological characteristics of PLAs. The results of the analysis of the FLA and ALA patients will be presented in a separate article. During the study period, the average annual incidence of hospitalization for a PLA was approximately 5.7 cases per 100 000 individuals. When ALA, FLA and HsLA cases are combined with PLA cases, the incidence of LAs increases to 8.9 cases

TABLE 10. Comparison of the treatments, clinical outcomes and mortality rates (MRs) of FLAs between patients with diabetes mellitus (DM) and without diabetes mellitus (non-DM)

MR/Treatments / Clinical outcomes	DM cases 18 (%)	Non-DM cases 33 (%)	p value
MR	7 (38.9)	5 (24.2)	0.085
Treatments			
Ab	2 (11.1)	2 (6.1)	0.607[a]
PD + Ab	11 (61.1)	12 (36.4)	0.090
SG + Ab	5 (27.8)	19 (57.6)	0.042
Outcomes			
m-TT	32.5 ± 17.3	26.3 ± 15.7	0.037[b]
LOS (day)	42.3 ± 25.6	34.7 ± 21.2	0.030[b]
PS	30.4 ± 18.5	28.7 ± 17.2	0.043[b]
AAT	37.9 ± 19.3	30.8 ± 18.6	0.052[b]

MR, mortality rate; Ab, antibiotic; PD, percutaneous tube drainage; SG, surgery; LOS, length of stay at hospital; PD + Ab, percutaneous tube drainage + antibiotic; SG + Ab, surgery + antibiotic; m-TT, mean tubing time; PS, persistence of symptoms (since patients accepted clinical treatments); AAT, antibiotic administration time.
[a]Fisher's exact test.
[b]Student's *t*-test.

per 100 000 individuals. The incidence rate of PLAs in this study is higher than that in previously published reports from Denmark, Canada and the United States, which indicated a PLA incidence rate of 1.1–3.6 cases per 100 000 individuals [1,3,4,14]. However, the incidence rate in this study is lower than that in Taiwan (17.6 cases per 100 000 individuals) [5]. The different aetiological factors for PLAs and the varying prevalence of disease in the biliary system, such as cholangitis and biliary calculi, could have caused the variation in the PLA incidence rates between these countries and China. In addition, the regional and climatic differences among these countries could have contributed to this variation. The association between PLAs and DM has been confirmed in a series of reports [7,8,12,13]; therefore, the different incidence rates of PLAs between adult patients in China and other countries may be the result of a varying prevalence of DM in these countries. From a clinical perspective, PLAs account for the highest rate of LAs. PLAs can be frequently observed in outpatient clinics or emergency departments, and the associated morbidity and mortality of PLAs exceed those of the other types of LAs, such as ALAs and HsLAs. Therefore, we aimed to elucidate the clinical characteristics, aetiological or microbiological features and outcomes of PLAs in this study. According to the results of the retrospective study, there are notable differences in the clinical characteristics, pathological changes, complications, microbiological features, outcomes and predictors of mortality between patients with DM and patients without DM.

In this study, we found that the mean age of PLA patients with DM was approximately 6 years greater (p 0.024) than that of patients without DM. The effect of ageing on the incidence of DM could have led to this difference. The mean age of most of the PLA patients was >57 years (diabetic patients, 63 years), which suggests that PLAs could be considered a type of senile disease. The elderly and individuals of advanced age are more susceptible to immune deterioration and increased morbidity, which may predispose them to PLAs, such as those that are associated with DM, cardiovascular disease and chronic obstructive pulmonary disease. Furthermore, these diseases in the elderly are usually long-term diseases, which may have a significantly negative effect on patient health. The relationship between decreased immunity and DM was demonstrated by the higher prevalence of the common cold in PLA patients with DM (p 0.039). DM is a risk factor for cardiovascular disease, and we found that diabetic PLA patients were more likely to develop CVSO than non-diabetic PLA patients (p 0.023). Similar to the results in previously published reports [7,8,12], our results suggest that DM is a risk factor for PLAs. Patients with DM (previously known or newly diagnosed) or any other underlying immunocompromised conditions, such as malignancy, viral infection or post-chemotherapy/radiotherapy, were more prone to develop a PLA than patients without them. Additionally, we observed that the male predominance in both of the PLA groups was consistent with previous reports [3,4,15–17].

After reviewing the correlative reports and integrating the results from this study, we conclude that the pathogenesis of PLAs has changed over the past decades. Previously, pylephlebitis and biliary disease were the two most common aetiologies of PLAs, but the incidence of these diseases has been decreasing [15]. In this study, cryptogenic infection was the most frequent aetiopathogenesis of PLAs, and this finding is consistent with previous reports [3,12,15,18]. DM interferes with neutrophil chemotaxis and phagocytosis [19–22]; however, the influence of DM on the function of macrophages remains unknown. In the recent histories (within 2 weeks) of the PLA patients, we found that the common cold was more frequent in the DM group than in the non-DM group but that malignancy was significantly more prevalent in the non-DM group than in the DM group (p 0.049). PLAs usually develop in immunocompromised patients; therefore, the acquisition of the common cold may be a signal of temporary immunodeficiency. From a clinical perspective, PLAs can be a secondary infection to a hepatic cyst, especially when patient immunity is insufficient, and DM contributes to the development of hepatic cysts into PLAs in immunocompromised individuals. This finding may explain why hepatic cysts were more common in the DM group than in the non-DM group. (Table 2).

Regarding pathogenesis, we found that cryptogenic PLAs accounted for most of the LAs in the cohort; however, the

rate of PLAs in the DM group was higher than that in the non-DM group. Biliary calculi and/or cholecystolithiasis were more common in the non-DM group, which may correlate with the high prevalence of biliary tract diseases in the non-DM group. The results of this study are consistent with the results in previously published reports [12]. Distant metastasis is a major origin of PLAs, and skin and soft tissue infections (SSTIs) are a source of distant metastasis. Patients with DM are prone to developing infective diseases, such as SSTIs, furuncles and carbuncles, which were found in both groups in this study. A greater number of these diseases were found in the DM group; however, there were no statistically significant differences between the two groups. (Table 2).

The majority of PLAs were located in the right hepatic lobe, which may be relevant to its anatomical position, size and propensity to receive the greatest amount of portal blood flow and lymphatic return. Compared with non-DM patients, bilobar involvement was detected in more diabetic patients, and the difference was statistically significant. In this study, we found that the sizes of most of the LAs were <10 cm. Compared with the non-DM group, the diameters of the abscesses in diabetic patients were more frequently larger than 10 cm. In addition, the prevalence of multiple abscesses in the DM group was higher than that in the non-DM group. All of the results reveal that the outcomes of PLA patients with DM are generally more severe than those of the patients without DM.

A gas-forming abscess is a less common type of abscess and is generally associated with a high mortality rate, accounting for 7–24% of all PLA cases [23]. In this study, gas-forming abscesses in the DM and non-DM groups accounted for 11.4% and 5.0% of the PLA cases, respectively. This difference was statistically significant; therefore, DM patients are more susceptible to gas-forming abscesses, and this conclusion confirms previous findings [12,23–28]. Diabetic patients, especially patients whose plasma glucose is poorly controlled, provided a beneficial environment for the growth of gas-forming microorganisms. Gas formation occurs as a result of mixed acid fermentation within abscesses by formic hydrogenlyase, which is an enzyme produced by microorganisms. Our study confirmed the higher fatality rate of gas-forming LAs. In our review, five patients out of the 28 patients who had a gas-forming abscess died of gas-forming PLAs. The general fatality rate of gas-forming abscesses is 17.9%, which is different from previously reported results [23,25]. The aetiology of the high fatality rate of gas-forming PLAs is unclear.

During hospitalization, the most common complication that occurred in both groups is bacteraemia, followed by CVSO, reactive pleural fluid (RPF), MODS and septic shock. Our results are consistent with previously published reports [12]. There is no statistically significant difference between the groups regarding the prevalence of bacteraemia and RPF, whereas the prevalence of CVSO in both groups is statistically different, and this finding confirms that DM is a risk factor for cardiovascular disease. The prevalence of MODS and abscess recurrence in the DM group is higher than that in the non-DM group. The total average febrifacient time (t-AFT) and the duration of stay in the ICU of diabetic patients are longer than those of the non-DM patients. These findings suggest that the clinical features, pathophysiological processes and prognoses of PLA patients with DM are generally worse than those in patients without DM. This result may be associated with the underlying immunocompromised condition of the DM patients.

Symptomatology of PLA

In this study, the most common symptoms were fever and/or chills, followed by nausea and vomiting, RUQ pain and general weakness. The typical triad of symptoms, including reported fever, chills and abdominal pain, was present in less than one-third of the patients in the two groups, and this finding is comparable with other studies [3,12,15,18]. This result may be related to the medications that were taken by patients prior to their hospital admission. Compared with non-DM patients, the temperatures of the patients with DM were more frequently >38.5°C, and the prevalence of SIRS and shock was higher in the DM group. These data suggest that the pathophysiological processes of PLAs in DM patients are more severe than those in non-DM patients. In addition, we observed that there were more PLA patients with DM who presented with nausea and vomiting than patients without DM. Nausea and vomiting often accompany ketoacidosis in DM patients; therefore, these symptoms may be associated with underlying ketoacidosis in DM patients upon admission to the hospital. Additionally, PLA patients may present symptoms and signs, such as weight loss, abdominal pain, diarrhoea, cough or dyspnoea, pleuritic or chest pain, rales or rhonchi, hiccups, ascites, hepatomegaly, jaundice and Murphy signs. These non-specific symptoms result in a delayed diagnosis of PLA; therefore, physicians should treat patients with these symptoms and signs promptly to prevent catastrophic outcomes.

Laboratory and imaging findings of PLA

In this investigation, the most predominant haematological or biochemical change in patients is CRP, which is an acute-phase protein that is synthesized by liver endothelial cells. In many studies, CRP has been demonstrated to be an ideal marker in determining the usage of antibiotics and assessing

the efficacy of antibiotics. CRP is considered to be a valuable indicator of inflammation [29–31]. In both groups, the CRP levels of approximately all of the patients were >6 mg/L, and these results are consistent with previous reports [12,17,32]. In addition, neutrophilic pleocytosis was present in both groups. Approximately 80% of the diabetic patients had high white blood cell counts (WBCc >10 000/dL), which were significantly different from those of the non-DM patients (69.3%). However, the prevalence of elevated neutrophil counts (>75%) in the DM group was lower than that in the non-DM group, which could be the result of DM interfering with neutrophil maturity, chemotaxis and phagocytosis [20,21]. The blood tests for the PLA patients with DM and without DM were similar: increased ALP, GGT and ESR; liver function changes; leukocytosis; hypoproteinaemia; anaemia; and prolonged PT. Most of the biochemical indicators were not significantly different between the groups; however, significant differences were found for albumin, ESR, serum glucose and WBCc. The blood levels of BUN and Cr, which are two parameters that indicate renal function in DM patients, were significantly different from those in the non-DM patients. This finding revealed that PLA patients with DM may have been more prone to contracting diabetic nephropathy, which usually damages host renal function, thereby increasing the blood levels of BUN and Cr.

We found that 88.6% of the diabetic patients and 90.1% of the non-DM patients had elevated neutrophil counts, which suggests that the neutrophil count is more sensitive than WBCc in the diagnosis of PLA. The associated application of these two biomarkers could assist physicians by reducing misdiagnoses of PLA and unnecessary use of imaging analysis. In addition, physicians should not exclude the presence of a PLA in patients who have normal WBCc and liver function tests. Remarkably, more than one-fourth of the patients presented with temple hyperglycaemia (>120 mg/dL) in the non-DM group, and stress hyperglycaemia may have accounted for this result.

Radiological examination is essential in the diagnosis of PLAs. Approximately 30% of the patients had positive chest X-ray findings. Pneumonia, right pleural effusion and elevated right hemidiaphragm were the main complications that were detected by X-ray. In this study, right pleural effusion and elevated right hemidiaphragm resulted in a misdiagnosis of PLA. In China, ultrasonography (US) and computerized tomography (CT) are the most frequently employed diagnostic modalities for PLAs. US and CT have demonstrated good accuracy; however, US has limitations, particularly when the abscesses are small, isoechoic and solitary. In this study, US had a sensitivity of approximately 96%, which was higher than that previously reported [33]. This sensitivity could have resulted from the advanced diagnostic skills and affluent clinical experiences of the sonographers. Simultaneously, the CT scan has a sensitivity of 98%, which is consistent with previously published reports. Magnetic resonance imaging (MRI) is generally employed as a stand-by option when a diagnosis is unclear. Similar to the ultrasonic findings, the CT results in positive patients usually show a hypodense area in the liver. There are no conclusive differences between the two groups according to the three imaging methods.

Bacteriology

In this study, *K. pneumoniae* was the most commonly isolated aerobe in the blood and pus cultures, followed by *E. coli* (Table 5 and 6). In the pus cultures, the rates of polymicrobial infections in the DM and non-DM groups were 16 (12.2%) and 14 (9.3%), respectively. Anaerobes accounted for 6.9% of the infections in the DM group and 1.3% in the non-DM group. This statistically significant result demonstrated that DM should be considered a high risk factor for anaerobic infection. In the blood cultures, we observed that the rate of positive growth was higher in DM patients than in non-DM patients (73.9% vs. 53.6%). *E. coli* was more commonly isolated in the non-DM group than in the DM group. In our hospital, to increase the rate of a positive blood culture when the body temperature of a patient was over 38.0°C, a blood sample was taken and cultured; therefore, there may be bias in the result. *Bacteroides fragilis* was the most frequently isolated anaerobic organism. In Europe [34] and North America [3,12], the most common pathogenic bacterium of PLAs is *Streptococcus milleri*; conversely, *K. pneumoniae* is the most commonly isolated pathogen in Asia, especially in Taiwan [16,17,25,35–37]. Our findings confirmed the findings from previous studies.

The prevalence of PLAs due to *K. pneumoniae* has been reported to be increasing worldwide [3,10,34,38–41]; however, the role of DM in the temporal shift in PLA epidemiology remains to be elucidated. In the pus and blood cultures, the prevalence of *E. coli* is higher in the non-DM group than in the DM group, which may be correlated with the high prevalence of BC or CC in the former. The systematic microbiological data in this study confirmed the previously documented opinion that DM is a risk factor for gram-negative bacteraemia, including episodes that are derived from abdominal foci of infection. The underlying biological mechanisms that are induced by DM may include tissue hyperglycaemia and a predilection for microorganisms, including Klebsiella species and *E. coli* [10,42–44]. The major mechanism for PLA development is the haematogenous seeding of the liver, mainly through the portal system. In addition, the circulation and local spread of infection within the abdominal

cavity are common pathogenic pathways. SSTIs, furuncles and carbuncles are observed in the past medical histories of several PLA patients, and these findings suggest that metastasis may play an important role in the pathogenesis of PLA.

In the bacteriological statistical results of this study, enteric gram-negative rods, including Klebsiella species, accounted for more than 80% of the PLA isolates; anaerobic bacteria accounted for <10% of the isolates; and gram-positive cocci accounted for more than 10% of the isolates in the non-DM group and <10% in the DM group. The most common gram-positive cocci and enteric gram-negative rods that were isolated from the pus of non-DM patients are *Viridians streptococci* and Klebsiella species, respectively. The difference is statistically significant. Compared with the non-DM group, patients with DM were more prone to infection with *K. pneumoniae* and anaerobes. These findings are comparable with those of previous studies of PLA [14,34,41,45]. Notably, other causes that were not as frequently detected, such as hydatid origin and fungal causes, were predisposing conditions for LAs in this present study. Moreover, we found that DM was a medical condition that was associated with FLAs. This result confirmed similar conclusions that were published in previous reports [46–48].

Bacterial drug resistance

K. pneumoniae and *E. coli* are the two most common pathogens in both groups; therefore, we conducted an additional analysis of their microbiological characteristics. According to the National Committee for Clinical Laboratory Standards (NCCLS), we tested the susceptibility and resistance of the two pathogens to the most commonly used antibiotics at the clinic using standard biochemical tests. The bacteriological statistical data indicated that the status of bacterial drug resistance in the DM group was more severe than that in the non-DM group, which suggests that DM was a potential cause of resistance. This finding is consistent with previously published conclusions [49]. The strains of *E. coli* that were isolated from PLA patients are commonly resistant to most of the first-line antibiotics that are used at the clinic, and a high rate of isolated *E. coli* strains was resistant to penicillins, quinolones, aminoglycosides, and first and second generation cephalosporins, such as ampicillin, piperacillin, ciprofloxacin, levofloxacin, gentamicin, cefoxitin and cefuroxime. The prevalence of ESBL-positive *E. coli* strains that were isolated in the DM group is higher than that in the non-DM group (p 0.005).

Many previous studies have demonstrated that the risk factors for antibiotic resistance or multidrug resistance correlated with clinical conditions, such as inappropriate initial empirical administration of antibiotics, increased antibacterial use, antibacterial abuse, continued or irregular prior administration of antibiotics before hospital admission, insufficient previous antimicrobial treatment, septic shock, haematological malignancy, recent hospitalization, recent use of similar antibacterial and mechanical ventilation and severe underlying diseases, such as DM and end-stage renal disease [49–52]. In addition, older age and underlying malignancy have been demonstrated to be risk factors for the development of antimicrobial-resistant isolates [27,53,54]. We did not investigate the relationship between underlying malignancy, age and MDR; however, we found that DM correlated with age (p 0.024). Additionally, DM was associated with antibiotic resistance. PLA patients with MDR were older than those without MDR; therefore, age may be a risk factor for the development of drug resistance. This conclusion is in agreement with previously published results [55].

The resistance of the *K. pneumoniae* strains that were isolated from PLA patients is significant, and these isolated strains are commonly resistant to most of the first-line antibiotics, such as penicillins, quinolones, aminoglycosides and first and second generation cephalosporins (for example, piperacillin, ampicillin, ciprofloxacin, levofloxacin, gentamicin, cefazolin and cefuroxime). Drug-resistant *K. pneumoniae* is more prevalent in the DM group than in the non-DM group. DM patients are generally immunocompromised, and their ability to combat invasive bacterial infections is decreased, which may compel physicians to increase the dosage of antibacterial drugs and prolong the duration of drug administration. Consequently, the prevalence of bacterial drug resistance increases. In China, inappropriate antimicrobial treatment is a common health problem, especially in community and private clinics and village, and town and country hospitals. Antibiotics are often prescribed to treat individuals even when the indications for the medication are lacking. PLA patients who receive antibiotic treatment at these locations would be susceptible to antibiotic resistance. In addition, a delay in the initiation of appropriate antibiotic treatment is another frequent health problem in China. This inappropriate use of antibiotics has been demonstrated to be associated with increased morbidity and mortality [56].

Similar reports on bacterial drug resistance are consistent with these results; however, there were several discrepancies [51,52,57]. The spectrum of the antimicrobial resistance pattern in this study was different from that observed in other hospitals [10], which may be correlated with the different policies regarding antibiotic use among the various hospitals and bacterial variation. *K. pneumoniae* and *E. coli* are the two most common pathogens of PLAs in this investigation. Regarding the antibiotic resistance profile of these pathogens and the high rate of resistance to antibiotics, the choice of these antibiotics or similar antibiotics should be

precluded in the initial empirical treatment of hospitalized PLA patients upon admission. The broad spectrum of antimicrobial therapy and drug combinations should be recommended and initiated before the pathogens are cultured and identified. A report from Taiwan revealed that all of the isolated *K. pneumoniae* strains from LAs remained susceptible to quinolones, aminoglycosides, sulphamethoxazole-trimethoprim, and all of the β-lactam antibiotics, excluding ampicillin and ticarcillin [10], and this conclusion is not consistent with the results of our study. Regional disparities may have accounted for the difference. In addition, the study in Taiwan was conducted approximately 12 years ago, and the trend for antimicrobial resistance has been drifted with policies regarding the use of antibiotics.

The first ESBL-producing strain of *K. pneumoniae* was documented in 1983 in Germany [58]. Subsequently, similar reports from Europe and the US were published [59,60]. Although the current global prevalence of ESBLs is unknown, their prevalence is increasing and their epidemic status is severe. It has been reported that 10–40% of *E. coli* and *K. pneumoniae* strains express ESBL in several parts of the world [61]. In this study, we found that the ESBL-producing strains of *E. coli* and *K. pneumoniae* were more common in the DM group and the rate of ESBL that was expressed in *E. coli* and *K. pneumoniae* is higher than that in the non-DM group. These findings suggest that DM may be correlated with the increasing rate of pathogenic ESBL-producing bacteria. To the best of our knowledge, this is the first report that describes the statistically significant differences in the prevalence of ESBL-producing strains of *E. coli* and *K. pneumoniae* between DM and non-DM groups. The outcomes of the patients who were infected with ESBL-producing organisms are usually poor because these organisms generally exhibit high-level resistance to antibacterials, which are used to treat them, and the mortality rate in these 'susceptibility/treatment mismatched patients' is higher [62–64]. ESBLs have been isolated from a variety of *Enterobacteriaceae* and *Pseudomonas aeruginosa* [65,66]. We also found similar results in this study, but being restricted to their rare isolates, we did not investigate them further.

Therapeutic regimen

To date, there is no definite consensus on the treatment of PLA. A report indicated that the effect of intermittent needle aspiration was equivalent to continuous catheter drainage, and needle aspiration was recommended as a first-line drainage approach [16]. However, a study in Singapore on PLAs that were >5 cm in diameter concluded that surgery provided better clinical outcomes than percutaneous drainage (PD) [37]. Most clinicians employ image-guided PD as first-line treatment for PLAs whereas surgery is employed as second-line treatment unless the conditions of the patient do not allow surgery to be performed [67]. Surgery is reserved only for severe or complicated cases, such as patients with advanced malignancy or larger and multiloculated abscesses [37]. PD and surgical treatments are not competing methods but have their own indications. Surgery is an alternative option for non-responders to percutaneous treatment. In this study, three predominant measures were undertaken to treat PLA: using antibiotics alone (Ab), combining percutaneous drainage with antibiotics (PD + Ab) and combining surgery with antibiotics (SG + Ab). In our hospital, initial empirical antimicrobial treatment is provided as soon as a clinical diagnosis of PLA is made. The empirical administration of antibiotics is usually prescribed as piperacillin plus amikacin and metronidazole, piperacillin/tazobactam plus metronidazole or cefepime plus metronidazole. However, if a patient presents the risk factors for infection with ESBL-producing organisms, carbapenem antibiotics (e.g. imipenem, meropenem, ertapenem or doripenem) should be recommended before the culture and isolation results are obtained. Once the blood or abscess fluid cultures and bacterial isolation tests are confirmed, antibiotic regimens should be narrowed and prescribed accordingly. On the basis of our clinical experience and the results of this study, we propose the following treatment algorithm: small (<5 cm) unliquefied abscesses should be treated with Ab alone; large (≥5 cm) uniloculated abscesses should be treated with PD + Ab; and large multiloculated and complicated abscesses should be treated with SG + Ab. Optimal measures should be selected according to the condition of the patient, treatment response and the characteristics of the PLA. In this study, 71.5% and 73.9% of the PLA patients were treated with PD + Ab in the DM and non-DM groups, respectively. The cure rates for the treatments in the DM and non-DM groups are 90.3% and 92.0%, respectively. The mortality of the PLA patients is 7.6% and 6.5% in the DM and non-DM groups, respectively, which is similar to the findings in previous studies [1,12].

Therefore, treatment options should be determined on an individual basis regardless of the presence of DM. We recommend the treatment of PLAs with PD + Ab as an optimal regimen, and treatment with Ab alone or with SG + Ab can be integrated when necessary.

Treatments and outcomes

As diagnostic imaging techniques, image-guided drainage applications and new antibiotics have improved, the treatments and outcomes of PLAs have significantly improved over the past several decades [16,68–71]. The mortality rate of PLAs in our retrospective study is similar to previous

studies [12,40,41], and DM is not one of the factors that increases the fatality rate of PLAs. CVSO, multiple abscesses, anaemia, uraemia, gas-forming abscesses, bacteraemia/septicaemia, polymicrobial infection, MDR, jaundice, total bilirubin level, high BUN, hypoalbuminaemia and time in the ICU (ICU-T) were all statistically significant prognostic factors for the mortality of PLAs in the univariate analysis. When these significant variables were obtained from the univariate analysis and subjected to the multivariate analysis, uraemia, gas-forming abscesses, MDR isolates and ICU-T were fitted to the stepwise logistic regression model. These results are in agreement with the results from previous reports [12,26,27].

In this study, uraemia, gas-forming abscesses and MDR isolates were associated with high mortality rates; however, ICU-T was associated with the highest mortality rate. The conditions of patients who are admitted to ICUs for an indeterminate duration are typically severe. A prolonged stay in an ICU increases the probability of exposure to broad-spectrum antibiotics, and opportunities for the cross-transmission of resistant bacteria among patients. These outcomes may explain why ICU-T was determined to be a prognostic factor for mortality in the univariate and multivariate analyses. Our analysis is consistent with previously published reports [72]. (Table 11).

Several limitations to this study should be acknowledged. The study is retrospective, and all of the data were collected from medical records. The patients were recruited from a medical centre that is located in northeast China. Although our results are comparable with a series of previous reports in other countries and regions, the results from this study may be incomplete. Therefore, more extensive analyses should be conducted to confirm the findings in this study. We excluded PLA cases that originated from liver cancers in the multivariate analysis, which may result in a deviation in the results of the multivariate analysis. Because of restricted research funding, we could only conduct a preliminary review of the other types of LAs, such as FLAs, ALAs and HsLAs; however, additional studies should be performed. Because of the word count restrictions in this article, we could not present more details regarding the other three LAs; however, we will present these details in a separate article. Several PLA patients were excluded from this study because their medical treatment data were missing or because they were transferred to other hospitals without

TABLE 11. Significant factors related to mortality in 357 patients hospitalized with PLAs according to the univariate and multivariate analyses

			Univariate analysis		Multivariate analysis	
Variables	**Category**	**Mortality (%)**	**Odds ratio (95% CI)**	**p value**	**Odds ratio (95% CI)**	**p value**
Diabetes mellitus	Yes	12/158 (7.6)	1.2 (0.5–2.7)	0.696	–	–
	No	13/199 (6.5)	1.0			
CVS occurrence	Yes	7/47 (15.0)	2.8 (1.1–7.2)	0.049	10.9 (0.6–186.4)	0.099
	No	18/310 (5.8)	1.0			
Uraemia	Yes	5/12 (41.7)	11.6 (3.4–39.8)	<0.001	8.7 (1.5–51.4)	0.017
	No	20/345 (5.8)	1.0			
Multiple abscesses	Yes	8/45 (17.8)	3.8 (1.5–9.3)	0.007	2.7 (0.7–10.3)	0.147
	No	17/312 (5.4)	1.0			
Bilobar involvement	Yes	7/63 (11.1)	1.9 (0.8–4.8)	0.256	–	–
	No	18/294 (6.1)	1.0			
Gas-forming abscesses	Yes	5/28 (17.9)	3.4 (1.2–9.8)	0.048	7.6 (1.2–47.4)	0.030
	No	20/329 (6.1)	1.0			
Bacteraemia/septicaemia	Yes	19/166 (11.4)	4.0 (1.6–10.2)	0.004	3.2 (0.8–13.2)	0.107
	No	6/191 (3.1)	1.0			
Polymicrobial infection	Yes	6/34 (17.6)	3.4 (1.3–9.3)	0.028	5.9 (0.3–124.7)	0.254
	No	19/323 (5.9)	1.0			
MDR isolates	Yes	14/87 (16.1)	4.5 (2.0–10.4)	<0.001	4.8 (1.2–18.7)	0.024
	No	11/270 (4.1)	1.0			
Jaundice	Yes	6/16 (37.5)	10.2 (3.3–30.9)	<0.001	14.1 (0.2–973.5)	0.221
	No	19/341 (5.6)	1.0			
T. Bil	≥5 mg/dL	21/173 (12.1)	6.2 (2.1–18.5)	<0.001	8.3 (0.1–525.4)	0.317
	<5 mg/dL	4/184 (2.2)	1.0			
BUN	≥22 mg/dL	10/126 (7.9)	1.2 (0.5–2.9)	0.610	–	–
	<22 mg/dL	15/231 (6.5)	1.0			
Haemoglobin	<12 g/dL	22/239 (9.2)	3.9 (1.1–13.3)	0.020	4.5 (0.8–24.7)	0.083
	≥12 g/dL	3/118 (2.5)	1.0			
Albumin	<35 g/dL	10/64 (15.6)	3.4 (1.5–8.0)	0.007	6.4 (0.5–89.6)	0.168
	≥35 g/dL	15/293 (5.1)	1.0			
t-AFT	≥15 day	6/59 (10.2)	1.7 (0.6–4.4)	0.445	–	–
	<15 day	19/298 (6.4)	1.0			
ICU-T	≥6 day	8/37 (21.6)	4.9 (2.0–12.4)	<0.001	9.1 (2.5–33.4)	<0.001
	<6 day	17/320 (5.3)	1.0			

OR, odds ratio; CI, confidence interval; CVS, cardiovascular system; MDR isolates, multidrug-resistant isolates; T. Bil, total bilirubin; BUN, blood urea nitrogen; t-AFT, total average fever time; ICU-T, stay in intensive care unit (days).

complete treatment at our hospital, which may have resulted in bias. Our analysis was restricted because the study was hospital based, and LA patients who were not hospitalized at our hospital were unintentionally excluded from the study, which may have resulted in a deviation in the results of the prevalence of LAs. Although the limitations in this study may apply to other similar hospital-based studies, their effect on the results of this study were probably minimal because our hospital serves a large population of individuals.

There are several advantages to this study when compared with previously published reports. The large and balanced sample collection ensures that the findings from this study have good generalizability and reliability. Our analysis included a complete evaluation of the signs and symptoms, underlying diseases, laboratory data, microbiological findings, radiographic features, complications, treatments and outcomes of LAs. This study was conducted in our hospital, which is the largest institution in northeast China. Our institution is an over 3000-bed tertiary care teaching medical centre that serves the Heilongjiang Province and several regions of Inner Mongolia and the Jilin Province. Our hospital provides more than 2 500 000 outpatient services, 220 000 emergency services and 30 000 surgical operations annually. All of the data from our analysis were subjected to univariate and multivariate analyses, in succession, and our conclusions were based on these analyses. A logistic regression model adjusted the results for other important factors, which made our conclusions more precise and comprehensive. We found that diabetic patients accounted for a high rate of the patients in the cohort of FLA patients, which indicated that DM plays an important role in the physiopathological process of FLAs. We presented a clear profile of the antibiotic resistance of pathogenic bacteria in PLAs, and reminded physicians that antibiotic resistance is a critical condition in the area in which this study was conducted. The data from this study suggest that third-generation cephalosporin or broad-spectrum antibiotic therapy should be recommended as the initial treatment for PLAs. Our analysis reveals that the microbiological spectrum of PLAs has evolved, and the predominant pathogens of PLAs are *K. pneumoniae* and *E. coli*.

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Transparency Declaration

The authors declare that they have no conflicting interests in relation to this work.

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